UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/086,637 | 03/04/2002 | Milton David Goldenberg | 018733-1094 | 8273 |

22428 7590 06/01/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

| EXAMINER | |
|---|---|
| HARTLEY, MICHAEL G | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1616 | |

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/086,637 | GOLDENBERG, MILTON DAVID | |
| | Examiner | Art Unit | |
| | Michael G. Hartley | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *99-201* is/are pending in the application.

4a) Of the above claim(s) *99-182,194,195 and 198-201* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *183-193,196 and 197* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/19/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

### *Election/Restrictions*

Applicant's election of Group VI (claims 183-197) in the response filed 4/8/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of the species wherein the label is In-111 and the antigen is CEA is further acknowledged.

Accordingly, claims 99-182, 194, 195 and 198-201 are withdrawn are not being drawn to the elected invention. (Note, claims 194 and 195 do not encompass the elected label, a radiolabel, In-111).

### *Response to Amendments*

The preliminary amendment filed 6/10/2002 has been entered.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 183-193, 196 and 197 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to describe the instantly claimed method wherein the detection is performed without the use of a contrast agent or substitution agent. The specification is silent to performing the claimed methods without the use of either of these agents and does not specifically describe this negative proviso. It is noted that original claim 23 does recite this negative proviso. However, claim 23 is a dependent claim on claim 1, that is drawn to a different method (e.g., the method of claim 1 using a divalent single chain antibody, as compared to a bispecific antibody as claimed, and claim 1 does not use a bivalent labeled hapten as claimed, as it uses a labeled antibody). Thus, clearly

the methods are different. The specification (including the original claims, namely claim 23) fail to describe the methods as claimed (the elected methods), using a bispecific antibody and a bivalent labeled hapten, with the exclusionary proviso that the detection is performed without the use of a contrast agent or substitution agent as now claimed. It is noted that any negative limitation or exclusionary proviso must have basis in the original disclosure. The mere absence of a positive recitation is not basis for exclusion.

The dependent claims fall therewith.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 183-193, 196 and 197 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 183, the recitation of "wherein said detection is performed without the use of a contrast agent" is confusing. Since the labeled hapten is being detected, and the label is "a diagnostic radioisotope, a MRI imaging enhancing agent or a fluorescent label" as set forth in claims 193+, clearly these labels are within the scope of "a contrast agent." Thus, it is unclear how a contrast agent can be excluded when a type of contrast agent is specifically being used for detection.

Also, in claim 183, the recitation of "subtraction agent" is confusing because it is unclear what is meant by this term. The specification fails to provide any definition or examples of a "subtraction agent" and such a term is not a well recognized term of art that gives the term a clear and defined meaning.

Claim 184 recites the limitation "the step of injecting said patient with a clearing composition" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Such a step of injecting a clearing composition is not present in base claim 183 and it is unclear if this is an additional step or what step it is further limiting.

***Claim Rejections - 35 USC § 103***

Claims 183, 187-189, 191-193, 196 and 197 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (USP 4,932,412) in view of Barbet (USP 5,256,395) in further view of Horowitz (US 4,706,652).

Goldenberg '412 discloses a method of detection of lesions during an intraoperative or endoscopic procedure comprising, 1) administering (injecting) to a patient an effective amount of a labeled antibody or antibody fragment which specifically binds a tumor antigen (such as, CEA, applicant's elected antigen) and detecting the presence of elevated levels of accreted label at the target site within 48 hours of said procedure, see column 2, lines 5-64. The methods further include combination therapies, such as, further including surgically removing lesions (e.g., tumors), the use of lasers, etc., see column 4, lines 24+. The antibody may be various types, including bispecific antibodies and fragments thereof, having CEA specificity, see columns 6-7. Various radionuclides may be used as the label, including In-111, applicant's elected species, see column 6.

Goldenberg fails to specifically disclose that the second binding site of the bispecific antibody binds a hapten and that a radiolabeled hapten is administered.

Barbet discloses a method of enhancing radiodiagnosis or radiotherapy which use antibodies by combining the methods with administration of a hapten which may be labeled with a radionuclide an using a bispecific antibody which has one binding site for a tumor and the other for the hapten, see columns 4-8 and example 4. Barbet teaches that the use of labeled hapten and bispecific antibody having binding sites for cancer antigen and the hapten improve the effectiveness of such radiodiagnostic/therapeutic procedures, see columns 8-9.

It would have been obvious to one of ordinary skill in the art to modify the methods of radiodiagnosis disclosed by Goldenberg by administering a radiolabeled hapten and a bispecific antibody having a second binding site to the hapten because it is known in the art that methods of radiodiagnosis using site specific radiolabeled antibodies can be made more effective by such a two step approach of

administering a bispecific antibody and a labeled hapten, wherein the bispecific antibody has a binding site for both the target (e.g., a cancer antigen) and the hapten. One of ordinary skill in the art would have been motivated to use the improved means accreting radiolabeled at the desired target site using hapten/bispecific antibodies as taught by Barbet to improve the effectiveness of the methods of radiodiagnosis disclosed by Goldenberg.

Claim 190 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (USP 4,932,412) in view of Barbet (USP 5,256,395), as taken above, in further view of Horowitz (USP 4,706,652).

While Goldenberg and Barbet teach that combination therapies may be employed in the radiodiagnosis and radiotherapy of tumors, they fail to specifically teach that the combination therapy includes brachytherapy delivered via a catheter.

However, brachytherapy is well known in the art as a method of treating tumors.

Horowitz teaches that brachytherapy by administering radioactive seeds via a catheter provides advantages of safer implants that allow the patient to be discharged, see columns 1-2.

It would have been obvious to one of ordinary skill in the art to use brachytherapy as one of the combination therapies in the methods disclosed by Goldenberg because Goldenberg teaches that various combinations of cancer therapy may be used and brachytherapy is a well known therapy for the treatment of tumors that is administered via a catheter to provide safe and effective cancer treatment, while allowing the patient to be discharged from the treatment center, as shown by Horowitz.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the

conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 183-193, 196 and 197 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,387,350. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the patent are very similar to those of the pending application. For the most part, the patented claims are within the scope of the instant claims. The claims differ only slightly, for example, the patented claims specify that a clearing step using a specific type of clearing agent within a specific time frame (within 24 hours), while the instant claims are open to a clearing step, which is present in dependent claims, but none of the pending claims recite the time frame (as in the patented claims). Since the claims are open to when the clearing agent may be injected, it would have been obvious to one of ordinary skill in the art to administer the clearing agent anytime prior to the procedure recited in the preamble, which is up to 48 hours after administration of the first component so that the clearing is effected prior to completion of the method to obtain the advantage of clearing the unbound antibody. Thus, it would have been obvious to administer the clearing agent within 48 hours which specifically encompasses the within 24 hours as claimed in the patent. Also, the dependent claims of the pending application state that the clearing agent may the same as those claimed. The instant claims also recite a negative limitation which is not recited in the patented claims; however, this limitation does not appear to limit the present methods to be a different method of the '350 patent, since the same detection techniques are employed, and the patented claims do not require the step that is excluded in the negative limitation.

***Conclusion***

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael G. Hartley whose telephone number is (571) 272-0616. The examiner can normally be reached on M-F, 7:30-5, off alternative Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael G. Hartley
Primary Examiner
Art Unit 1616

5/27/2004